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Antiphospholipid Syndrome: A Case Demonstrating Diagnostic Challenge

To the Editor: Antiphospholipid syndrome (APS) is defined as recurrent thrombosis together with (1) moderately to highly elevated serum anticardiolipin antibodies, or (2) a prolonged phospholipid-dependent clotting test such as activated partial thromboplastin time (APTT) that does not normalize upon mixing patient with normal plasma. We report a case of recurrent thrombosis associated with an ill-defined autoimmune disease. Despite the clinical picture markedly resembling APS, standard APTT was repeatedly normal, and anticardiolipin antibodies were normal to only mildly elevated. The diagnosis was finally made on the basis of prolonged APTT, using rabbit brain phospholipid with silica instead of bovine brain phospholipid with ellagic acid, and on positive hexagonal phase phospholipid antibody neutralization test (HexPPANT).

A previously healthy white man presented with pulmonary embolism and two episodes of blue toe at age 57. Then, with coumadin, he was well until 1 year prior to death, at age 61. During the last year of life, he suffered from recurrent bouts of presumably autoimmune pancreatitis. An extensive workup for other causes of pancreatitis and for known autoimmune diseases was unyielding. The following nonspecific abnormalities were present: enlarged pancreas without pseudocysts, calcifications or dilated ducts by CT, ANA 1:320, ESR >100 mm/hr, lymphocytopenia (0.6–0.9 $\times$ 10^9/L), anemia (hemoglobin 80–130 g/dl), thrombocytopenia (90–150 $\times$ 10^9/L), hypocellular marrow (80–90% fat, 10–20% hematopoietic cells), and anergy by skin tests.

Four months prior to death, the patient stopped coumadin for 3 months. During this period, he developed two transitory ischemic attacks, adrenal insufficiency, livedo reticularis, platelet count drop to 60 $\times$ 10^9/L, and serum creatinine elevation to 3.5 mg/dl with microscopic erythrocyturia and proteinuria (3.7 g/day). Renal angiograms revealed amputation of renal artery branches, suggesting thromboembolism. CT disclosed wedge-shaped areas of renal cortical thinning, suggesting infarcts. Renal biopsy showed multiple arteriolar and capillary thrombi. Anticardiolipin IgM was normal on two determinations; anticardiolipin IgG was once 11 GPL (normal) and once 19 GPL (mildly elevated) (ELISA). Prothrombin time was normal on 5/5 determinations. APTT using bovine brain phospholipid with ellagic acid (Activated Thrombofax, Ortho, Raritan, NJ) was normal on 4/5 determinations and slightly abnormal on 1/5 determinations (patient 29, control 25 sec). APTT using rabbit brain phospholipid and silica (Auto APTT, Organon-Teknika, Durham, NC) was moderately prolonged (patient 55, control 34, 1:1 mix, 44 sec). Dilute Russell Viper venom test (Bioclot, Biopool, Burlington, Canada) was normal (50 sec, normal 31–54 sec). HexPPANT (Staclot, American Bioproducts, Parsippany, NJ) was moderately abnormal (16 sec, normal <10 sec). Antithrombin III, protein C, protein S, and inhibition of factor V by activated protein C were normal.

Reinstitution of coumadin resulted in stabilization of serum creatinine and normalization of platelet count (>150 $\times$ 10^9/L on three determinations). The patient died during a bout of epigastric pain. Autopsy was not done.

This report supports the following approach to the diagnosis of APS. First, a battery of tests rather than a single test should be performed whenever APS is clinically suspected. This may be due to the heterogeneity of antiphospholipid antibodies or the high interlaboratory variation in test results [1–3]. Second, because of their high sensitivity, a silica-based APTT and HexPPANT should be included into the battery [4,5].

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An "All-Oral" Combination Therapy in Chronic Lymphocytic Leukemia Including the Oral Idarubicin

To the Editor: Oral idarubicin (IDA) has been evaluated as a single agent and in combination in acute myeloid leukemia (AML), and a substantial antileukemic effect has been demonstrated [1,2]. In low-grade non-Hodgkin lymphomas (NHL) IDA is now being utilized along with chlorambucil (CLB) and dexamethasone (DEX) to assess efficacy and toxicity when used as primary treatment [3]. However, to the best of our knowledges, studies dealing with the use of oral IDA in chronic lymphocytic leukemia (CLL) are virtually absent [4].

We treated six CLL patients considered resistant to conventional chemotherapies (CLB ± PDN, four cases; vincristine, cyclophosphamide, prednisone ± doxorubicin, two cases) in advanced clinical stage (stage B, 4, stage C, 2), median age 64 years (range, 55–76 years) with a "fully oral" combination, including IDA 12 mg/m^2 on days 1, 3, and 5, CLB 20 mg (total dose) on days 1–3 and prednisone (PDN) 50 mg (total dose) on days 1–5. Cycles were repeated every 28 days.

Preliminary results on the toxicity and efficacy of this "all-oral" regimen administered on an outpatient basis, after informed consent was achieved, are presented here. In all instances, therapy was well tolerated. After a median number of four courses of treatment (range, 1–5), no cardiotoxicity was clinically noted. Alopecia was not a problem. Despite the absence of antiemetic prophylaxis, neither acute nor delayed emesis was observed. Infectious toxicity (WHO, 2) could be demonstrated in a single patient. According to the National Cancer Institute (NCI) [5] response criteria in CLL, two patients were considered in partial remission (PR), three patients who did not show any change of pretreatment clinicohematological features were evaluated to meet criteria of stable disease (SD), progressive disease

TABLE I. Patient Characteristics

Patient	Age	Sex	Previous therapy	Before				After				Response[a] (mo)/toxicity (WHO)	Cycles (no.)
				Stage	BM	Hb (g/dl)	Lymph (10^9/L)	Stage	BM	Hb (g/dl)	Lymph (10^9/L)		
1	71	M	CLB-PDN	IV-C	D	10.1	14.9	IV-C	D	9.4	12	SD-11	4
2	76	M	CLB-PDN-EDX	IV-C	D	10.2	139	II-A	ND	11.3	55	PR-11	4
3	61	M	COP	II-B	non-D	13.2	11.9	II-B	ND	11.4	10.8	SD-14	4
4	67	M	CHOP/ CLB-IFN/RT	IV-C	non-D	9.5	12.4	IV-C	ND	7.3	28	PD (WHO-2, inf)	1
5	55	F	CLB-PDN	III-B	ND	10.8	212	II-B	ND	12.2	154	PR-7	5
6	59	M	CLB	II-B	non-D	12.9	18.3	II-B	ND	13	17	SD-1	4

ND, not done; PD, progressive disease; SD, stable disease; PR, partial remission; COP, cyclophosphamide, oncovin, prednisone; CHOP, COP plus doxorubicin.
[a]According to NCI criteria (Cheson et al. [5]).

(PD) was registered in one patient. Median time to disease progression for patients in PR or SD was 9 months (range, 1–14 months) (Table I).

The results of the present study, although based on a small number of patients, are in keeping with good compliance with this novel "fully-oral" drug regimen, including IDA given on alternate days. By contrast, the administration of IDA on alternate days, producing long-standing but lower peaks of idarubicinol (IDAol), the active metabolite, may result either in reduced toxicity or in enhanced antineoplastic activity [1].

Finally, the tendency for physicians treating patients with low-grade malignancy to prefer combination regimens suggests that oral IDA combined with alkylating agents could be worthy of exploration, particularly in elderly patients who are less disposed to receive more intensive regimens. This is especially true in CLL disease, in which dose intensity and schedule are not mandatory for delivering therapy with curative intent.

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In Vivo CAMPATH-1 Monoclonal Antibodies: A Novel Mode of Therapy for Acute Graft-Versus-Host Disease

To the Editor: CAMPATH-1 is a rat antihuman monoclonal antibody (MAb) that recognizes the CDw52 cell surface marker, an antigen expressed on the surface of nearly all normal and malignant human lymphocytes but not found on normal hematopoietic stem cells [1]. Exposing bone marrow cells (BM) to CAMPATH-1 in vitro results in substantial in vivo depletion of T cells, due to the removal of T cells bound to the IgG2b MAb by the recipients Fc receptor-positive reticuloendothelial cell system following infusion of the BM [2].

It is known that BM treatment with CAMPATH-1, which results in sufficient removal of donor T cells effectively prevents graft-versus-host disease (GVHD). Studies have demonstrated that anti-T-cell MAb can be used for the prevention and treatment of GVHD, as mature donor T cells play a dominant role in the induction of GVHD [1]. Recently, CAMPATH-1 has been administered in vivo, as part of the pre-bone marrow transplantation (BMT) conditioning, in an attempt to prevent graft rejection, for remission induction in patients with resistant lymphoid malignancies and for the treatment of severe autoimmune disorders, especially rheumatoid arthritis [3]. In addition, antithymocyte globulin and anti-interleukin-2 (IL-2) receptor antibodies have occasionally been used successfully in steroid-resistant GVHD [4].

CAMPATH-1 may therefore be of theoretical benefit in treating aGVHD. We describe a CML patient with grade IV GVHD, with major consequences to the liver who responded to CAMPATH-1 administration and 4 years post-BMT with minimal chronic GVHD. We conclude from the case presented that CAMPATH-1 administration may be of benefit in the treatment of aGVHD.

A 40-year-old woman with Philadelphia (Ph)-positive CML in first chronic phase was admitted for allogeneic BMT. The conditioning included cyclophosphamide (60 mg/kg × 2), 1,200 cGy total body irradiation (200 cGy × 6) and i.v. CAMPATH-1G (kindly provided by Dr. G Hale and Dr. H Waldmann, Cambridge, UK), 10 mg/day for 4 days pre-BMT. She received non-T-cell-depleted BM (3.38×10^8 viable cells/kg) from her HLA-matched, MLC nonreactive sister. As anti-GVHD prophylaxis, the patient received i.v. Cyclosporin A (3 mg/kg/day).

Engraftment occurred with a white blood cell (WBC) count of $>1.0 \times 10^9$/L on day +22, ANC $> 0.5 \times 10^9$/L on day +24, and untransfused platelet count $>25 \times 10^9$/L on day +30. Post-BMT, the patient had become Ph-chromosome negative. At $1\frac{1}{2}$ months post-BMT, she developed grade IV GVHD manifested by skin rash (biopsy-proven) and disturbed liver function tests (LFT). Oral Cyclosporin A (6 mg/kg/day) and p.o. prednisone 1 mg/kg/day was introduced without improvement. She was hospitalized 3 weeks later due to progression of the grade IV GVHD with liver dysfunction (ALT 348 U/L, AST 172 U/L, ALP 410 U/L, GGTP 1,123 U/L, and bilirubin 284 μmol/L). She was treated with i.v. Cyclosporin A (3 mg/kg/d) and i.v. solumedrol (5 mg/kg/day) for 3 days with no response. The patient's LFT deteriorated dramatically (ALT 434 U/L, AST 110 U/L, ALP 735 U/L, GGTP 1,190 U/L, billirubin 787 μmol/L, albumin 28 g/L).

Because of the patient's unresponsiveness to conventional treatment, I.V. CAMPATH-1G (10 mg/day) was administered for 4 days, which caused fever, chills, and response to antipyretics. Following CAMPATH-1, LFT began to return to normal, bilirubin first, followed by ALT and ALP, which gradually diminished 10–14 days later (Fig. 1). One month after initiation of CAMPATH-1, LFT showed the following results: ALT 192 U/L, AST 61 (U/L, ALP 328 U/L, GGTP 1,347 U/L, and bilirubin 36 μmol/L. On a maintenance dose of Cyclosporin A and prednisone, skin manifestations